The cost-effectiveness of losartan versus captopril in patients with symptomatic heart failure

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of angiotensin converting enzyme (ACE) inhibitors in the treatment of symptomatic heart failure in older patients. These inhibitors may be designed to prevent an increase in levels of bradykinin.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Individuals aged over 65 years requiring treatment for symptomatic heart failure, New York Heart Association Class II, III, or IV with ejection fraction \( \leq 40\% \). Patients who had previously received ACE inhibitor or angiotensin II antagonist treatment were excluded from the analysis.

Setting
Community and hospital. The economic analysis was conducted in Ann Arbor, Michigan, USA.

Dates to which data relate
Effectiveness and resource data were collected between May 1994 and June 1996. 1997 price data were used.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Cost data were collected prospectively using the same patient sample as in the clinical analysis.

Study sample
352 patients were randomised to receive losartan with 370 patients receiving captopril. The population sample used in the trial was appropriate, as symptomatic heart failure is increasing most significantly in more elderly populations. Power calculations were used to determine the sample size - 90% power to detect 40% reduction in persistent renal dysfunction events, assuming a rate of 30% for such an event in the captopril group.

Study design
This was a multi national double blind randomised controlled trial carried out in 125 centres. The duration of follow up
was until the end of the trial - a period of 50 weeks. Randomisation was stratified by age. 65 patients (18%) in the losartan group and 111 (30%) patients in the captopril groups did not complete the course of treatment, although they were still followed up for mortality and morbidity data.

Analysis of effectiveness
The analysis of effectiveness was based on the intention to treat. The primary health outcomes used in the clinical study were level of renal dysfunction in patients, adverse events and mortality rates. At analysis both patient groups were shown to be comparable in demographic and clinical characteristics.

Effectiveness results
There was no significant difference in the level of renal dysfunction between patients in the two groups. Patients in the losartan group had a significantly reduced risk of mortality compared with those receiving captopril (4.8% compared with 8.7% (p=0.035) which appears to have been due primarily to a reduction in sudden cardiac deaths. Excluding death, there were significantly fewer adverse events leading to discontinuation in the losartan group 43 (12.2%) compared with 77 (20.8%) in the captopril group, (p=0.002).

Clinical conclusions
Tolerability of losartan was improved compared to that for captopril and, furthermore, losartan reduced the risk of mortality compared with captopril. There was, however, no difference in the incidence of renal dysfunction between the two groups.

Modelling
Survival and costs per patient beyond the 48 week duration of the clinical trial were calculated. These were used to generate long term cost-effectiveness ratios. The authors assumed that age/sex adjusted mortality rates would be proportionally greater than those for the general population, and it was assumed that patients enrolled in the trial would continue to consume resources at the same rate as in the trial and that, at point of death, they would also use additional resources at the same rate as those consumed by non survivors within the trial.

Measure of benefits used in the economic analysis
The benefit measure was years of life gained.

Direct costs
The costs of medications, hospitalisations, and emergency room visits were estimated. Some costs and quantities were reported separately. The cost of hospitalisations was based on the number of hospital days and the average Medicare cost per hospital day ($1,051 per day). Emergency room visit costs were also taken from average Medicare payments. The costs of medications in the study were taken from a 1998 sample of medical utilisation and costs in the United States. Costs were estimated from the perspective of a third party payer and a discount rate of 3% per annum was applied to costs. Information on utilisation of services and quantities of medication used was gathered separately from cost data. It was assumed that patients who discontinued treatment had no additional medication costs.

Statistical analysis of costs
Non parametric bootstrapping was performed, 1,000 bootstrap resamples being run. Probabilities that cost-effectiveness ratios were less than some notional threshold e.g. $50,000 per life year gained, were estimated.

Indirect Costs
Not included.
Currency
US dollars ($).

Sensitivity analysis
Average life expectancy following the trial was varied between 1 and 12 years, costs of medications were reported using four different cost schedules, hospitalisation costs were estimated on a DRG basis as well as on a per day basis. The costs for outpatient visits and non-study medications were also considered.

Estimated benefits used in the economic analysis
In the base case scenario the incremental number of life years gained for patients in the losartan group was 0.190 (undiscounted). Average life expectancy of survivors was estimated to be 5.5 years. Side effects of treatment were included in the analysis.

Cost results
In the base case scenario with an average life expectancy of 5.5 years following the trial, lifetime costs for patients were estimated to be $34,693 for losartan compared with $33,924 for captopril. The incremental cost of using losartan was therefore $769. The costs of adverse events and subsequent treatment were included in the analysis.

Synthesis of costs and benefits
The incremental cost per life year gained using losartan compared with captopril was $4,047. In sensitivity analysis changes in the cost of captopril had a significant impact on the cost-effectiveness ratio, in the worse case scenario using Medicaid federal upper limits for captopril reimbursement the incremental cost per life year gained increased to $14,058. The probability that losartan would be cost effective compared to captopril, given an acceptable intervention threshold of $50,000, was 0.82 - only slightly less than in the base case scenario (0.88).

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator used in the clinical study, namely that the ACE inhibitor Captopril had previously been shown to have fewer renal effects than longer lasting ACE inhibitors. Furthermore this was the only trial to compare losartan with an ACE inhibitor.

Validity of estimate of measure of benefit
Effectiveness data were taken from a well-designed randomised controlled trial, and the study sample was representative of the population at greatest risk of heart failure, namely elderly patients. Furthermore the clinical paper points out that this group is often under represented in studies recruiting more broadly in the general population. Both patient groups were shown to be comparable at analysis. The analysis was conducted on an intention to treat basis. Estimates of benefits were obtained from the effectiveness analysis and were extrapolated over patient long-term life expectancy. This choice of estimate was justifiable. Only one third of the study sample were women, and the authors of the clinical paper note that the effectiveness of losartan in the female population requires further investigation. The ACE inhibitors in the clinical study were reported, however, to be used in less than 30% of patients with heart failure because of the possibility of complications, despite their overall benefits. The authors (of the clinical study) noted though that further studies would be required to compare losartan against other longer lasting ACE inhibitors.

Validity of estimate of costs
All categories of costs relevant to the perspective adopted were included in the model, although the costs of outpatient visits and non-study medication were considered only in sensitivity analysis, where they had little impact. The authors did not consider costs to others in society or informal care costs, which could be substantial for an elderly cohort of patients. Some of the costs and quantities were reported separately. Resource use quantities were obtained prospectively from the clinical study. A statistical analysis of quantities was performed. Quantities of medication and hospital
services required were assumed to be the same over remaining lifetime following the completion of the trial for all patients who continued to comply with treatment. Prices were obtained from published sources and a sensitivity analysis of prices was conducted. Dates and prices years used were reported and charges were not used to proxy costs.

**Other issues**
Comparisons with other studies were limited, as this trial was the first to compare losartan with an ACE inhibitor, however trials examining the effectiveness of other interventions for the treatment of heart failure were reported. The issue of generalisability to other settings was not specifically addressed, although the trial was conducted in 125 different centres. It would have been interesting had the authors examined the cost-effectiveness of the intervention using cost data from other non-US participants in the trial. However the authors may have presented their results selectively since they state that both events and costs were discounted, whereas only the ratio between undiscounted benefits and discounted costs was presented in the paper. The authors acknowledged a number of limitations in their analysis; firstly that a lack of long term data meant that they had to assume that long-term resource utilisation was consistent with that observed in the trial (accounting for additional resource use at time of death). Furthermore costs of outpatient medical visits and non-study medication were excluded, although these were examined in sensitivity analysis. The lifetime expectancy assumptions made by the authors were also varied in sensitivity analysis, without impact. The relatively small size of the patient sample in a trial where the primary endpoint was not mortality, but renal dysfunction is also a limitation.

**Implications of the study**
Further evaluations should be conducted comparing the effectiveness of losartan against a range of ACE inhibitors.

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